Docket No.: 04266/100M275-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amedeo Leonardi

Application No.: 10/768,953 Confirmation No.: 4561

Filed: January 29, 2004 Art Unit: 1614

For: Treatment of Neuromuscular Dysfunction . . . Examiner: Leslie A. Royda

PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In accordance with the Pre-Appeal Brief Conference Program, Applicants hereby request a pre-appeal brief panel review of the final rejection mailed June 14, 2007 in the above-identified patent application.

The present Request is filed concurrent with the filing of a notice of appeal and before the filing of an appeal brief. No amendments are being filed with this request. A request for an extension of time and a check for the required fee are filed herewith, to extend the time to reply to the aforementioned final rejection to December 14, 2007.

Review is requested for the following reasons:

I. COSFORD AND BONNEY DO NOT MAKE A *PRIMA FACIA* CASE OF OBVIOUSNESS

[A] The Facts

Claims 1-8, 11-18, 28-30, 41 and 42 stand rejected under 35 U.S.C. § 103(a). Claims 19 and 20 are allowable but objected to as dependent from rejected claims. The narrowest of the rejected claims is claim 42, which is directed to the treatment of a neuromuscular dysfunction of the lower urinary tract ("urinary neuromuscular dysfunction") in a mammal in need of such treatment by administration of an effective amount of the compound MTEP, which is an antagonist of the metabotropic glutamate receptor subtype 5 ("mGluR5"). The rejection relies upon: 1) Cosford (WO 01/16121), which discloses MTEP and states that the compounds disclosed therein, amounting to 183 species, provide a

method for treating schizophrenia; and 2) Bonney (Bonney, WW, et al., 1997, Schizophrenia Res. 25, 243-49), which states that of 63 patients undergoing long-term hospitalization and treatment for schizophrenia, 23 (37%) reported experiencing symptoms of urge incontinence.

[B] The Examiner's Rationale of the Rejection

The rejection is not made under § 102 but under §103(a). Hence, the rationale of the rejection is not that Cosford inherently anticipates the use of MTEP for the treatment of urinary neuromuscular dysfunction. The Applicant's understanding of the rationale of the rejection is limited by the omission of specific findings of the *Graham* factors, in particular Applicant does not understand what is deemed to be the difference between the invention and the prior art.

Nonetheless Applicant's best understanding of the rationale of the rejection is that Cosford allegedly suggests the treatment of schizophrenics with MPEP and that Bonney shows some patients having schizophrenia suffer, in addition, from urinary neuromuscular dysfunction. It allegedly follows then that Cosford inherently suggests the administration of MTEP to some subject having urinary neuromuscular dysfunction.

Neither Cosford nor Bonney expressly teach that MTEP is therapeutic for urinary neuromuscular dysfunction, rather such a benefit would be inherent in the administration of MTEP for schizophrenia. See Advisory Action p. 2, ¶ 5, ("[W]hatever effect[s] the instantly claimed MTEP compound has in treating urinary incontinence must necessarily be present in the method disclosed by Cosford.") Hence, an inherent suggestion is deemed sufficient to make a *prima facie* case of obviousness.

[C] The Combination of Bonney and Cosford Does Not Provide a Reasonable Expectation of Success and Is Not *Prima Facie* Evidence of Obviousness

While the co-occurrence of urinary incontinence and schizophrenia was obviously recognized by one of ordinary skill at the time of the invention, that MTEP has any beneficial effects on urinary incontinence was not. However, in contrast to anticipation, precedent forbids basing the *prima facie* case of obviousness on the unrecognized properties of the prior art. *In re Spormann and Heinke,* 363 F.2d 444, 150 USPQ 449 (CCPA 1966) ("As we [have] pointed out [previously] the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicted on what is unknown."). *Compare In re Napier,* 55 F.3d 610, 34 USPQ2d 1782 (Fed. Cir. 1995) (recognized inherent properties can be used to show obviousness). The principle of *Spormann* has been recently reaffirmed in a slightly different context. *Aventis Pharma Deutschland v. Lupin Ltd.,* 499 F.3d 1293, 84 USQ2d 1197, 1204 (Fed. Cir. 2007) ("[A] puri-

fied compound is not always *prima facie* obvious over [a] mixture [that contains it]; for example, it may not be known that the purified compound is present in or an active ingredient of the mixture, ...")

The elements of *prima facie* obviousness have been laid out by the Federal Circuit in the context of a validity challenger's burden most recently as:

> [T]he burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so. [cites to CAFC omitted]; *see also KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 [82 USPQ2d 1385](2007) (a combination of elements "must do more than yield a predictable result"; combining elements that work together "in an unexpected and fruitful manner" would not have been obvious).

PharmaStem Therapeutics v. Via-Cell, 491 F.3d 1342, 83 USPQ2d 1289,1301-02 (Fed. Cir. 2007). *See also Velander v. Garner,* 348 F.3d 1359, 68 USPQ2d 1769 (Fed. Cir. 2003) (elements as between parties in an interference). Applicant respectfully submits that the elements of an examiner's *prima facie* of case obviousness have been and remain the same as set forth in *PharmStem*, although the required level of proof is not the same. *In re Vaeck,* 947 F2d 1438, 20 USPQ2d 1438 (Fed. Cir. 1991). A reasonable expectation of success is a state of mind. A reasonable state of mind cannot be based on what is not known. Therefore, the unrecognized, but inherent properties, of the prior art cannot provide a reasonable expectation of success.

Applicant further submits that the reasonable expectation of success must apply to the purpose recited by the claims, not some other purpose. When a specific clinical indication and therapeutic purpose is recited by a claim, the Applicant's objective intent is that it be a material limitation and the claim is so construed. *Jansen v. Rexall Sundown,* 342 F.3d 1329, 68 USPQ2d 1154 (Fed. Cir. 2003); *See also Rapoport v. Derment,* 254 F.3d 1053, 59 USPQ2d 1215 (Fed. Cir. 2001) (use of a drug to cure sleep apnea is patentable in view of the prior art administration of the drug to reduce anxiety associated with sleep apnea). The pending claims cannot read without inclusion of the clinical diagnosis of the subject of the claimed method. The rejection is improper because the rationale reads a material limitation out of the claims.

The impropriety of the rejection is apparent when one considers the implications of the rationale. While Bonney provided a numerical value of the overlap between the reference's indication, schizophrenia, and the claimed indication, urinary neuromuscular dysfunction, there is no authority which would attach any legal significance to the numerical value. A claim is obvious if any subject matter within its scope is obvious. What fraction the obvious subject matter constitutes of the whole has no legal effect. Consequently, if the rationale of the rejection is legally correct, then any probability greater

than zero of the co-occurrence of the two indications would suffice to show obviousness. Essentially all second medical-use claims could be found *prima facie* obvious. Exceptions would require that indications be mutually exclusive, as for example, if the referenced indication and claimed indication occurred in different age groups.

Accordingly, Applicant respectfully requests reconsideration of the rejection, because the rejection improperly reads a material limitation out of the claims, improperly relies upon the unrecognized inherent properties of the prior art to establish a reasonable expectation of success and is incompatible with the well-established application to the medical arts of the principle that a new use for an old compound is a patentable invention.

II. The Rejection is Improper because a Person of Ordinary Skill Would Not Follow Cosford's Teaching

Cosford is stated to teach that MTEP would be effective to treat schizophrenic patients. Applicant does not traverse for purposes of this appeal, but submits that such teaching is not legally sufficient. Because the rationale of the rejection requires that Cosford motivate one of ordinary skill to treat schizophrenia with MTEP, the relevant question is whether Cosford's teachingw would have been accepted as obviously correct by one skilled in the art or are supported by experimental data, the same standard that an examiner applies to the utilities disclosed by an applicant.

Applicant believes that the examiner relies for the stated teaching upon the second and third full paragraph of page 3 of Cosford. There the invention is disclosed to provide methods of modulating excitatory amino acid receptors including metabotropic glutamate receptors. The diseases that are suggested treatable by such modulation include not only schizophrenia but also include cerebral ischemia, psychiatric disorders, mood disorders, obesity, disorders of respiration, motor control and function, skin disorders, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia and astrocytoma. There is an equally broad list of disorders whose prevention is provided by the invention. It is not clear whether Cosford predictions of utility are affected by whether compounds act as agonists or antagonists, or whether they affect excitatory amino acid receptors generally, only metabotropic glutamate receptors including mGluR5, or specifically modulate mGluR5. In short, the list of diseases recited by Cosford is so broad and the basis for expecting therapeutic utility is so vague that no person skilled in the art would find plausible any teaching of Cosford. Therefore, a teaching of Cosford would be followed only if it were supported by data.

Applicant notes that results from three experiments were reported: a test for inhibition of glutamate-stimulated Ca^{++} influx using hmGluR5 transfected cells; a test for inhibition of glutamate-stimulated phosphatidylinositol hydrolysis, also in hmGluR5 transfected cells; and a test of *in vivo* an-

algesia. The compounds for which data are presented can be divided into four groups: those which are not "active" in any test; those active in the Ca^{++}-influx test only; those active in both *in vitro* tests; and those active in all tests. These data show that the compounds of the invention are functionally heterogeneous. There is no teaching in Cosford concerning which group of compounds is useful to treat schizophrenia and which not. Moreover, no experimental evidence or theoretical basis is provided by Cosford to link the modulation of mGluR5, as evidenced by any test, with the treatment of schizophrenia. Applicant respectfully submits that the teaching that any of the disclosed compounds would provides an effective treatment for schizophrenia would not be regarded as credible by one skilled in the art.

For the reasons given above Applicant respectfully submits that the person of ordinary skill in the art would not be motivated by Cosford to use MTEP to treat schizophrenia.[1]

Conclusion

For the foregoing reasons Applicant respectfully requests a review of the rejection of all of the pending claims with the exception of claims 19 and 20, which have not been rejected. Applicant requests the withdrawal of the rejection if the review determines that the rejection is contrary to law and/or not supported by the evidence of record.

Dated: December 14, 2007

Respectfully submitted,

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[1] During the preparation of this paper, the undersigned first became aware of the publication concerning MTEP, Cosford, WD, et al., 2003, J. Med. Chem. 46, 204-06, which is believed E-published on December 12, 2002. The undersigned does not regard Cosford 2003 as a non-cumulative, material reference, nor is this an admission that Cosford 2003 is prior art. However, the Examiner may want to consider whether Cosford 2003 suggests the use of MTEP to treat anxiety disorders.